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Distribution of REM Latencies and Other Sleep Phenomena in Depression as Explained by a Single Ultradian Rhythm Disturbance

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Summary: The McCarley-Hobson model, describing the alternation of NREM and REM sleep in the cat, was applied to human electroencephalographic data. The influence of initial conditions on oscillatory behavior was especially emphasized. It appears that the distribution of REM latency in depression, the abnormal accumulation of REM sleep, the variability of NREM-REM cycle duration, the frequent stage shifts, and frequent awakenings can be explained in this model by means of a decrease in the initial value of a single variable, which may be regarded as representing the strength of REM inhibition. The observation of slow wave sleep deficiency in depression may well be another reflection of this parameter. **Key Words:** REM sleep—Depression—Slow wave sleep—Ultradian rhythm.

Numerous polygraphic studies have revealed that the sleep profile of endogenously depressed subjects is characterized by a shortened latency of rapid eye movement sleep (REMS), a relative overproduction of REMS in the first third of the sleep period, a reduction of slow wave sleep (SWS, i.e., stage 3 and 4), frequent stage shifts, frequent intermittent awakenings, and a higher incidence of REMs, especially in the first hours of sleep (1). The shorter REM latency, in particular, is considered to represent a specific feature of primary affective disorders (2,3). Vogel et al. (4) suggested that the abnormalities in REMS production in depression are caused by disturbances in an ultradian oscillator that regulates the NREM-REM alternations. The ultradian oscillator was assumed to be of the same nature as the one described for NREM-REM sleep regulation in the cat by McCarley and Hobson (5) and Hobson et al. (6). In this model the oscillatory capacity is thought to be achieved by the reciprocal interaction of two elements, one excitatory and active during REMS, the other inhibitory and predominantly active during NREMS (Fig. 1). Vogel et al. (4) postulated that three aspects of this NREM-REM oscillator system are disturbed in depression: the strength of self-excitation of the REM-active part, the strength of the inhibition by the NREM-active part, and the power of the NREM-active part at sleep onset. The McCarley-Hobson model, however, provides a different interpretation of sleep abnormalities in depres-

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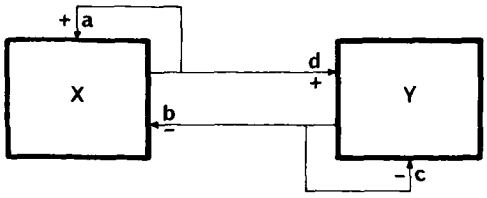

FIG. 1. Diagram of the NREM-REM oscillator model proposed by McCarley and Hobson (5). The variable x simulates the course of the discharge rate of cells in the pontine reticular formation in the cat, whereas the variable y describes the discharge pattern generated by locus coeruleus neurons. The excitatory and inhibitory pathways are indicated; the strength of these interactions are denoted by the parameters a, b, c, and d.

sion which is more satisfactory because of its greater simplicity and wider explanatory scope. This interpretation will be described in the present paper. A number of considerations have been taken into account.

Schulz et al. (7,8) and Coble et al. (9) have shown that the decrease in REM latency found in primary affective disorders is based on a bimodal distribution of latencies. Rapid eye movement sleep periods start either shortly after sleep onset (sleep onset REM periods—SOREMPs) or after approximately 55 min, i.e., with a latency only slightly shorter than in normal subjects (approximately 65 min). A comparison of nights with and without SOREMPs (10) reveals that it is only the SOREMP nights that show an initial overproduction of REMS. Differences of REM accumulation appear to be restricted mainly to the first hour of sleep. On the other hand, SWS production was found to be reduced, irrespective of whether the night was characterized by a short REM latency. Furthermore, the cyclic alternation of NREM and REM periods is more variable in depressives than in normals (11,12). It will be shown by computer simulations that the McCarley-Hobson model provides an adequate explanation of these features, including frequent stage shifts and awakenings, by assuming only an initially deficient REM inhibition in the NREM-REM regulating oscillator.

NREM-REM oscillator

On the basis of neurophysiological data, McCarley and Hobson (5) constructed a mathematical model that describes the ultradian rhythmicity of sleep in the cat in considerable detail. In this model the solutions of two coupled differential equations describe the discharge rates of two groups of cells in the cat brain. One group of cells is located in the gigantocellular tegmental field (FTG) of the cat pontine brainstem. These cells increase their discharge rate during REM episodes (6). A reciprocal discharge pattern is observed by the same authors in the other group of cells, located in the region of the locus coeruleus (LC). The model is formulated by a Lotka-Volterra set of equations:

$$dx/dt = ax - bxy$$
$$dy/dt = -cy + dxy$$

These equations describe an excitatory-inhibitory interaction such as shown in Fig. 1. The variable x represents the discharge behavior of the gigantocellular tegmental field cells, whereas y describes the firing behavior of the locus coeruleus neurons.

At a certain moment in time the locus coeruleus cells are subjected to a lateral excitation at a strength proportional to the firing rate x and the excitation strength d. Simultaneously, the locus coeruleus cells experience self-inhibition at a strength proportional to the constant c. Whether y will increase or decrease is dependent on the relative magnitudes of these two influences. Suppose that, at a given moment, x is small. This means that the self-inhibition of the locus coeruleus cells will be the most important influence on y and that y will decrease. As a consequence, its lateral inhibition of the tegmental field cells will decrease, and x will have a tendency to increase. An increase in x is supported by its self-excitation and increases

the excitatory influence on y. At the moment that $d \cdot x$ exceeds c, the value of y will no longer decrease but will start to increase. In this way it is easily seen that the system behaves like an oscillator, the properties of which depend not only on the parameters a, b, c, and d but also on the initial values of x and y.

It is not known whether the human ultradian sleep oscillator has a substrate similar to that proposed for the cat. Apparent differences in sleep structure exist between cats and humans. The cat usually wakes up after termination of a REM episode, whereas human subjects enter another NREM episode. Therefore, the firing rates modeled by the variable y are linked differently to sleep stages in cats and humans. As a consequence, we must point out explicitly that the application of McCarley-Hobson's model to human electroencephalographic (EEG) data is not based on electrophysiology, but that such application must be regarded as a phenomenological approach. In spite of this lack of neurophysiological evidence, the ability of this kind of model to describe human data still can contribute to functional understanding.

Simulations

The application of the McCarley-Hobson model of REM generation implies the solution of the set of coupled differential equations. This has been carried out numerically by means of a computer program.

In humans the absence of neurophysiological data eliminates the possibility of determining model parameters by directly fitting model predictions to actual discharge patterns. Fortunately, however, there is an extended area in the parameter space where parameter values influence model predictions only quantitatively.

We therefore simply accepted values proposed by McCarley and Hobson (5) in our simulations: $a = 0.549$; $b = 0.055$; $c = 0.2745$; $d = 0.02$. The initial values of x and y (known further as x_0 and y_0) were varied. Figure 2 shows three examples of resulting courses of predicted cellular discharge. In this figure x_0 is kept constant ($x_0 = 8$) and y_0 is varied. Note that the amplitudes of the discharge oscillations depend on the initial value y_0. Obviously, the model predicts only discharge rates of cells as a function of time, and an additional assumption is needed to predict the occurrence of REM episodes. On average, REM episodes began when the discharge rate of the tegmental field cells reached one-third of their maximum firing rate (5) (Fig. 2). We have therefore simulated the NREM-REM cycle by assuming that REMS was initiated whenever x reached 33% of its maximum value. The latency of the first REM episode is indicated in Fig. 2 by horizontal bars. Rapid eye movement latencies were expressed in terms of the elapsed fraction of the NREM-REM

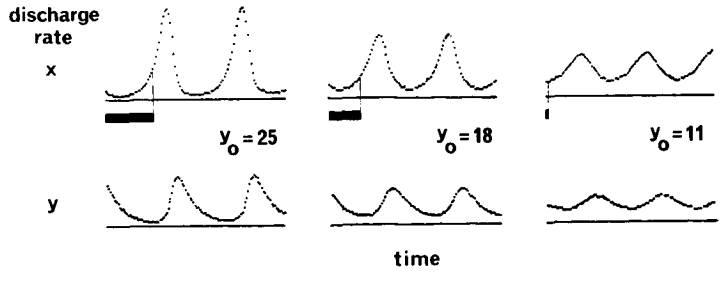

FIG. 2. Discharge pattern, obtained by simulation. At the onset of the simulation, the value of x was set at 8. The parameter values were $a = 0.549$; $b = 0.055$; $c = 0.2745$; $d = 0.02$. Horizontal bars in the figure indicate REM latencies. It is assumed that REM sleep is initiated whenever the discharge rate x reaches 33% of its maximum value.

cycle. These appear to have little dependence on x_0. However, y_0 strongly influences REM latency. Figure 3 shows REM latency as a function of y_0 for three distinct values of x_0. It is evident that very short REM latencies are predicted at lower values of y_0. Furthermore, at intermediate values of y_0, REM latency increases steeply with increasing y_0.

Our study is focused predominantly on the explanation of REM latency distributions. However, REM period duration is another aspect of the model that may be of interest. Hence, we need an extra assumption to define the end of a REM period from the course of x. Since cats usually awaken at the termination of a REM period whereas humans enter another NREM period, the analogy of NREM-REM regulation in cats and humans may not be valid at this point. For the moment we have defined the termination of the REM period to be the time at which x reaches its maximal value. We shall return to this point in the discussion.

NREM-REM cycle durations

So far we have expressed REM latencies as a percentage of the ultradian cycle duration. To calculate REM latency distributions, we must express latencies in minutes. To this end, data published by Spiegel (13) are very useful. This author described in great detail sleep data from 170 nights for 57 healthy elderly people. The age of the subjects ranged from 55 to 70 years, which corresponds to the age of approximately 50% of our population of endogenous depressives. From Spiegel's data we determined that the NREM-REM cycle lasts an average of 108 min, with a standard deviation (SD) of 25 min.

It must be noted that Spiegel concluded that the cycle duration varies over the night. In contrast, we find that Spiegel's data strongly support a constant NREM-REM cycle duration throughout the night. Admittedly, the first cycle is systematically shorter than the other cycles, but this is trivial, because the first cycle is measured from sleep onset and not from the termination of a REM period as are all others. According to Spiegel, the third and subsequent cycles become progressively shorter as compared with the second cycle. However, this result may be a statistical artifact, because the third and subsequent cycles do

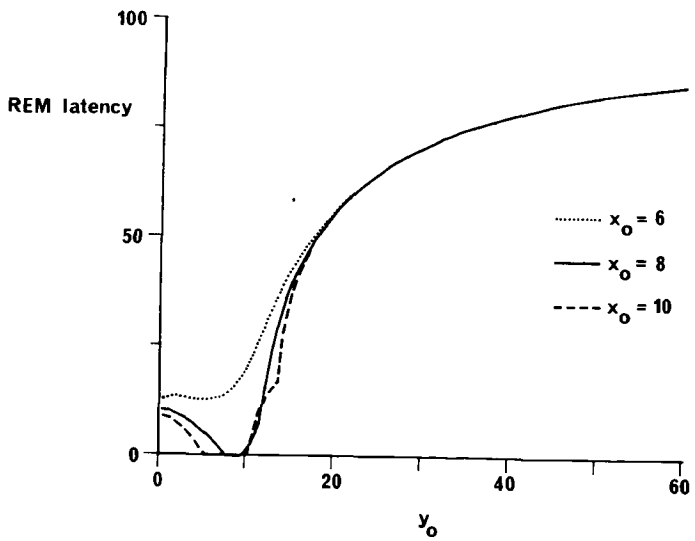

FIG. 3. REM latency (expressed as a percentage of cycle duration) as a function of the initial value of y is plotted for three distinct initial values of x.

not occur in every recorded EEG. The probability of the occurrence of short cycles, therefore, increases toward the end of the night, leading to shorter mean values. This fact becomes extremely evident by examination of a cumulative plot of Spiegel's data (Fig. 4). The graphs present the number of cycles shorter than the time indicated on the abscissa. Cycles 2, 3, and 4 occur equally frequently for durations up to 110 min. The graph strongly suggests that cycle 4 is very likely not to be completed when it lasts longer than 110 min. In such cases sleep was terminated by the experimenter. From these results we conclude that NREM-REM cycles are of intrinsically constant duration throughout the night.[1]

REM latency distribution

The empirical range of cycle durations has consequences for the model. According to the model, a specific value of y_0 leads to a strictly determined value of REM latency, expressed as a percentage of cycle duration (Fig. 3). Rapid eye movement latency expressed in *minutes* is found by multiplication of this percentage with cycle duration. Since NREM-REM cycle durations have an approximately gaussian distribution, each value of y_0 leads to one REM latency value (in minutes) from a range of possibilities, the distribution of which is again gaussian.

Using these assumptions it is possible to simulate the REM latency distribution in a fictitious population of subjects.

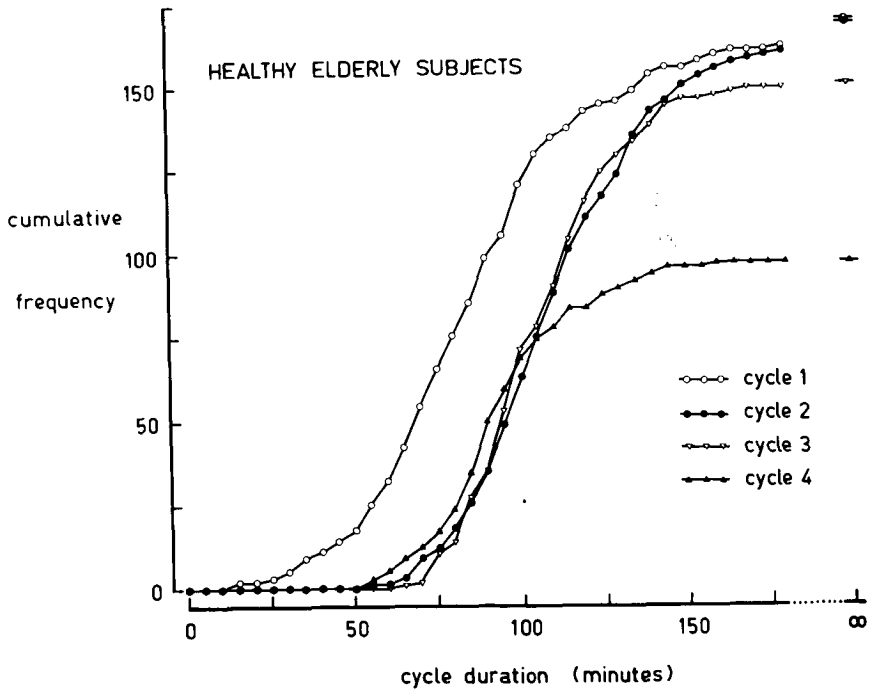

FIG. 4. The number of nights (from a total of 170) in which a specified NREM-REM cycle had a duration that was shorter than the time indicated on the abscissa. Data from Spiegel (13).

[1]In several nights in Spiegel's data cycle 3 or 4 or both began with more than 30 min of wakefulness. This period was not included by Spiegel in his calculation of the cycle duration. However, excluding this initial period of wakefulness leads to short cycle durations. Including the time of wakefulness would lead to abnormally long cycle durations. To overcome this problem we have omitted cycles with more than 30 min of initial wakefulness.

This is done by the following mathematical procedure: first, the distribution of y_0 values in the population (approximated by a gaussian function) must be specified by its mean and standard deviation. The probability of occurrence of any value of y_0 in the population can thus be found from the distribution curve. According to Fig. 3, each of the y_0 values leads to a certain REM latency value, expressed as a percentage of NREM-REM cycle duration. The probability of such a REM latency value equals the probability of finding the corresponding y_0 value in the population. Subsequently, the apparent range in NREM-REM cycle duration must be accounted for. On average NREM-REM cycles last 108 min, with a SD of 25 min. The conversion of REM latency values from percentages to minutes, therefore, leads to a smoothing of the REM latency curve.

The results of these calculations are presented in Fig. 5 and compared with actual empirical results. Figure 5a shows the distribution of REM latencies in the previously mentioned 170 nights for healthy subjects (data from ref. 13), together with the model simulations in which y_0 has a mean of 25 and a SD of 7. The selection of this y_0 distribution curve, which was done by trial and error, led to a satisfactory fit between the model simulation and the empirical data. The similarity of the distributions, however, is not especially surprising. A gaussian distribution of an input parameter will always lead to a roughly gaussian distribution of the results, as long as the model operates near its linear range. Apparently, this is a realistic possibility in the case of Spiegel's data.

Matters are different when REM latencies in depression are considered. In Fig. 5b (bars) experimental data compiled by Coble et al. (9) are presented. This study concerns 733 sleep recordings collected in 22 drug-free patients suffering from primary depression. The distribution of REM latencies is bimodal, which confirms the earlier findings of Schulz et al. (7,8). Rapid eye movement periods start either immediately after sleep onset or after

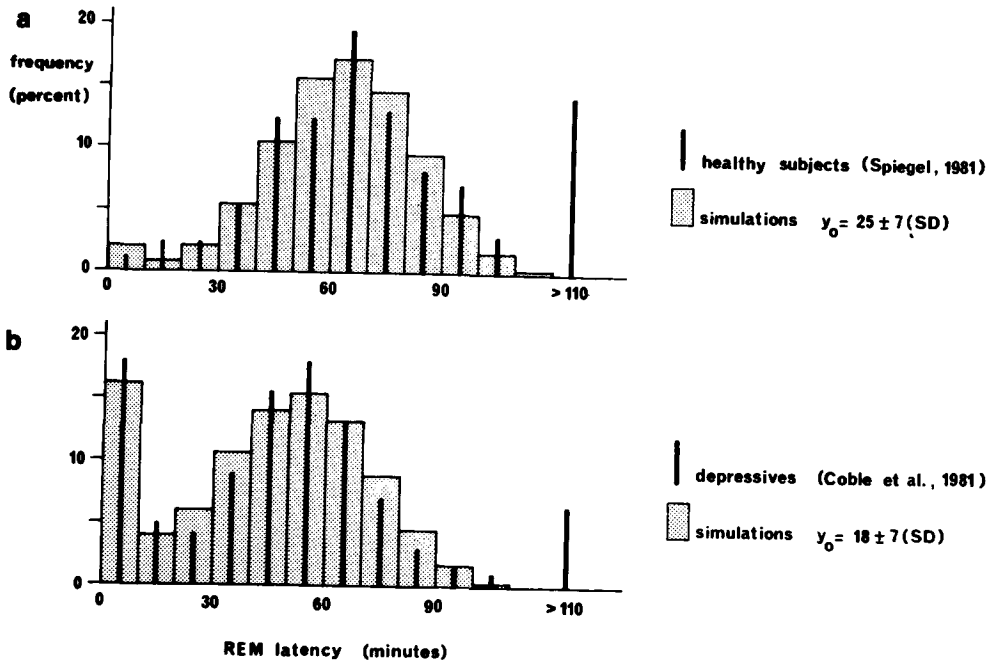

FIG. 5. The distribution of REM latencies. Fig. 5a: Comparison between model simulations and healthy elderly subjects. b: Comparison between model simulations and depressed subjects.

almost normal latencies. This latter peak in the distribution occurs after a slightly shorter latency than the peak found in a healthy population (55 versus 65 min). The distribution is not only the result of between subject variability but also of day-to-day variations *within* subjects. Individual primary depressives show both short and normal latencies. Figure 5b also shows the results from model simulations. The fit was obtained by selecting $y_0 = 18$ and SD = 7. The empirical distribution is simulated in its entire shape. Even the slight leftward shift of the main peak with respect to the peak in Spiegel's data is predicted by the model as a consequence of lower y_0 values. Day-to-day variations in y_0 are sufficient to explain the variations in REM latency (either short or nearly normal) in a series of nights for one depressed patient.

Further consequences

We have shown that the McCarley-Hobson model offers a detailed reproduction of REM latency distributions as measured in healthy subjects and also in depressed patients. For that purpose there was no need to select parameter values different from those chosen by McCarley and Hobson (5) to fit neurophysiological data from the cat. The only parameter that had to be varied was the initial value y_0, a start condition of the oscillator.

Our interpretation of the disturbance of the timing of REMS may elucidate some further phenomena characteristic of sleep physiology in depression. It is a well-documented fact that primary or endogenously depressed patients produce, on average, more REMS in the first third of the sleep period (4,14). This can be explained, firstly, by the fact that REMS starts earlier in many nights and, secondly, by the duration of the first REMS period. As to the first factor, in a previous study (10) we compared the REMS distribution over the night in nights starting with SOREMPs and in nights with (nearly) normal REM latencies. The latter nights turned out to show a virtually normal distribution of REMS over the night, as compared with young and elderly healthy subjects. Only the SOREMP nights yielded an abnormal REMS distribution, i.e., they showed an increased REMS production, which was restricted to the *first hour* of sleep.

Thus the above-mentioned overproduction of REMS in the first third of sleep can be explained in part by the existence of a timing disturbance of REMS at the beginning of sleep. Regarding the second factor (i.e., the duration of the first REMS period) we performed the following analysis. In Fig. 6 we plotted the duration of the first REMS period for endogenously depressed patients as a function of REM latency. The data presented are partly derived from a previous study (10) and partly from a study by Schulz et al. (7).

The continuous curve represents the relationship between REM latency and duration of the first REM episode predicted by the model at various initial values of y. Although the data scatter widely, it is evident that short episode durations are observed after both short and normal REM latencies, whereas long episode durations tend to occur more after short and intermediate REM latencies. This is precisely what the model predicts. The model therefore accounts for the average overproduction of REMS in the first third of the sleep period, since it predicts the early start of REMS in some nights, as well as the tendency to a longer duration of REMS after relatively short latencies. The quality of the resemblance between the data and the theoretical curve in Fig. 6 depends strongly on the assumption that defines the link between the course of x and the termination of a REM period. The choice of termination of REM at peak values of x differs from the definition given by McCarley and Hobson (5) for the cat and, in fact, is quite arbitrary. Since there is no independent way of verification, we wish to stress that it is mainly the *qualitative* fit that is of importance. The model explains the large range of REM durations at short REM

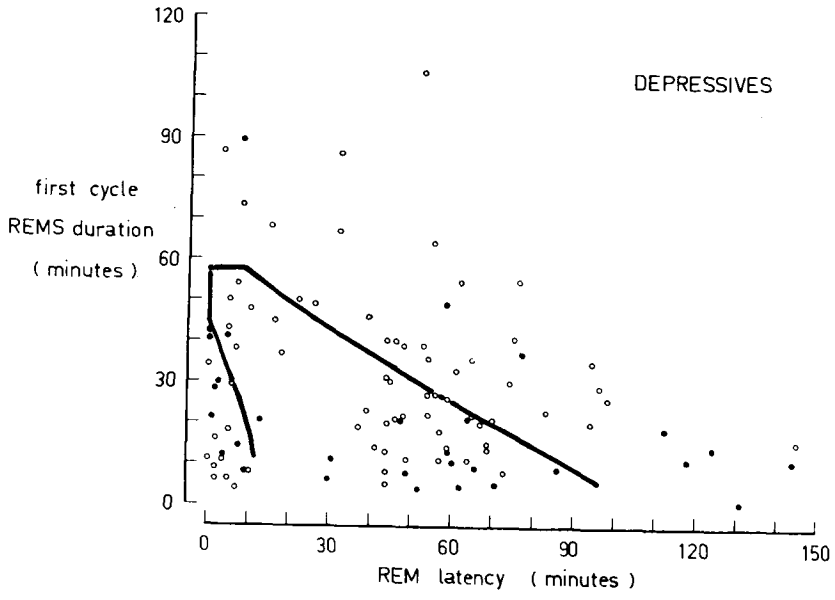

FIG. 6. The relationship between the duration of the first REMS period and REM latency. Continuous curve is that predicted by the model. Black dots represent our own measurements; open circles are extracted from the data of Schulz et al. (7).

latencies, the long REM durations at intermediate latencies, and the average decrease of REM duration on further increasing latencies. For the distribution of REM latencies observed in healthy elderly subjects (Fig. 5a), the model predicts an average REM duration of 12 min at an average latency of 66 min. For the distribution of REM latency in depression the similar values are 31 min for REM duration and 47 min for REM latency, respectively. The ratio of these REM durations (in both cases) is 1.4, which is close to the value reported by Vogel et al. (4) for the ratio of REM duration in depression versus controls.

Apparently, only the start condition y_0 of the oscillator needs to be varied to describe the timing of REMS in depression. The intrinsic excitatory-inhibitory interaction may therefore be undisturbed in depressed people as compared with healthy subjects. This conclusion is opposite to that formulated by Vogel et al. (4). These authors suggested that in addition to a reduced y_0 the self-excitation and lateral inhibition of the "x-cells" would be disturbed in depression. We agree with Vogel et al. that these assumptions enable the description of a shorter mean REM latency in depression equally well. However, as we have shown, these assumptions are redundant. The difference in REM latencies between depressed subjects and controls is most simply explained by a reduced y_0 alone.

In passing, it may be noted that these findings yield evidence contradictory to the opinion that a persisting phase shift of the REMS production rhythm in relation to other physiological rhythms could be of pathogenetic importance in endogenous depression (14). Depressive patients show a short lasting overproduction of REMS only in the first hour of some of their sleep periods. The only persisting feature is a deficiency of SWS, which may be related to a low initial value of y. Relatively small day-to-day variations in this value can lead to large variations in REM latency and duration of the first REMS episode and thus to incidental abnormalities in REMS distributions.

The model can also explain some additional physiological sleep characteristics. In other studies we have shown that NREM-REM cycle variability is larger in depressives than in controls (11,12). This empirical result is compatible with the assumption of only a reduced *initial* value y_0. Small fluctuations of y_0 near $y_0 = 18$ (simulating sleep in depression) lead to fluctuations in REM latency and REM duration 2.3 times larger than similar fluctuations of y_0 near $y_0 = 25$ (simulating sleep in healthy controls). The larger NREM-REM cycle variability can also be explained from Fig. 2, which shows that the predicted amplitudes of the discharge oscillations of FTG and LC cells decrease in conditions of decreased initial values of the discharge rate of the LC cells. The driving power of an oscillator usually decreases with decreasing amplitude of the oscillation. Therefore, a greater cycle variability in depression is consistent with the assumption of a lower initial value of y. In addition, the increased number of stage shifts and awakenings in depression can be interpreted as being caused by the same decrease in oscillation amplitude.

COMMENTS

Apparently, a number of EEG phenomena in depression can quantitatively or qualitatively be explained by the model in terms of reduced initial values of y. It is worthwhile, therefore, to relate the variable y to some observable physiological process. In the cat, y describes the cellular discharge pattern of neurons in the locus coeruleus. In humans, individual cellular discharges cannot be recorded. As a consequence we have tried to link the variable y directly to a physiological process, which is expressed in the EEG recordings.

In humans the first hour of sleep mainly consists of SWS and REMS. Where in the model the variable x is directly linked to REMS (by definition), it seems logical to surmise that the variable y is related to SWS production. However, y increases during REMS and is maximal at the onset of NREMS, whereas SWS begins several minutes later. The assumption, therefore, does not hold because of the asynchrony between experimental and theoretical curves. On the other hand, we have some preliminary data suggesting that a certain degree of inertia is present during the initiation of SWS. Arousals during SWS are usually followed by 10 to 30 min of NREMS, characterized by increasing EEG power. More rapid restorations of SWS are not apparent in our EEG data. This effect may explain the difference in timing between the discharge rate y and the occurrence of SWS. If this is the case, the initial value of y may still correspond with "NREM pressure."

Some recent models for the regulation and timing of human sleep assume the existence of a sleep regulating variable S, the value of which would be reflected in NREM power density (15–17). Borbély and Wirz-Justice (18) proposed that depressive sleep symptomatology is caused by a deficiency in the build up of S during wakefulness. The reduced initial value of y, necessary to describe REM latencies in depression, may be linked to S and therefore may reflect a reduced tendency to produce SWS. Depressives generally do show a reduced SWS production. On the other hand, SWS reduction is also found in insomniacs (1), who do not show short REM latencies. This is an argument against our hypothesis that SWS is directly linked to y, although one can imagine that SWS deficiency in insomniacs merely represents a by-product of sleep interruptions, whereas SWS deficiency in depression could be of a more intrinsic nature. This question remains to be answered.

Short REM latencies are reported not only in depression but also in narcolepsy (19,20). Preliminary data on the distribution of REM latency in narcolepsy (Van den Hoed, personal communication) indicate that this REM latency distribution may be different from the

distribution in depressives. It is possible that alternative model parameters could explain such a distribution. So far, we have insufficient detailed information on REM latencies and NREM-REM cycle durations in narcolepsy to make simulations worthwhile.

Changes in REMS period duration in the course of the night, which are much more pronounced in humans than in cats, are not described by the model. The model generates a persisting oscillation, with no changes in amplitude.

In humans, however, overnight changes in the frequency of REMs are extremely evident. In healthy subjects the incidence of REMs is small at the beginning of the night and increases progressively toward the end. Depressed subjects frequently also show a high incidence of eye movements at the beginning of the night. Hobson et al. (6) observed in the cat that REMs during REMS coincide with increased discharge rates of gigantocellular tegmental field cells. Nevertheless, they have not yet incorporated such fine detail into their model, nor did we. The model should first be extended to describe overnight changes in REMS duration before refinements describing REM density become worthwhile. For the present study, it seems more important to realize that REM density is by no means a measure of REM intensity (21). Instead, it seems to represent a measure of satiety or level of arousal. It therefore probably will not depend strongly on the state of the ultradian oscillator, but, most likely, on circadian and homeostatic mechanisms. Such processes certainly influence the process of REMS production, since a clear correlation exists between the amount of REMS and the circadian phase of the body temperature rhythm (22–25). There are experimental conditions in which sleep is shifted to an abnormal phase of the temperature cycle, leading to the occurrence of short REM latencies in healthy subjects. Such observations (23–25) are of great interest to the present study, but they can only be dealt with after incorporation of circadian and homeostatic influences into the ultradian model system.

Although modeling ultradian rhythmicity in humans cannot build on neurophysiological data obtained from structures within the brain, we believe that our model calculations support the view that in depressives, the distribution of REM latencies, the instability of the ultradian NREM-REM cycle, the frequent stage shifts and awakenings, and the reduced SWS production may all be consequences of one and the same disturbance in the ultradian rhythm generator.

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